PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 001-PCT-1	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/PL 03/00099	International filing date *(day/month/year)* 01.10.2003	Priority date *(day/month/year)* 04.10.2002
International Patent Classification (IPC) or both national classification and IPC C07J21/00		
Applicant PRZEDSIEBIORSTWO FARMACEUTYCZNE ANPHARM S.A. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.04.2004	29.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Guspanova, J Telephone No. +49 89 2399-7834

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/PL 03/00099

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-32 as originally filed

Claims, Numbers

1-9 received on 04.10.2004 with letter of 29.09.2004

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☒ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☒ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-9 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-9
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item IV
Lack of unity of invention

The application as originally filed related to the following separate inventions which were not so linked as to form a single general inventive concept:

1. Process for the preparation of steroid compound tibolone of formula 1 (independent claim 1).
2. Intermediate compounds of formula 2 (independent claim 17).
3. Process for the preparation of compounds of formula 2 as intermediates useful for the preparation of steroid compound of claim 1 (independent claim 21).

The application as originally filed has been restricted to the only one invention drawn up in amended claims 1-9 filed with the letter dated 29.09.2004, which claims are considered unitary

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. **Amendments**

The amendments filed with the letter of 29.09.2004 appear to satisfy the requirements laid down by Article 19(2) PCT, since support could be found in the description as well as in the claims as originally filed.

1. **Novelty**

The present application discloses a process for the preparation of tibolone of formula 1 (claims 1-9).

The essential technical feature of the process presently claimed is the hydrolysis in the presence of a salt of transition metals or salts of lithium or magnesium.
The processes for the preparation of tibolone disclosed in the cited prior art differ from

that of the present application in that they do not comprise the essential technical feature mentioned above. Therefore, the subject-matter of the present claims 1-9 are considered novel according to Article 33(2) PCT.

2. **Inventive step**

The problem underlying the present application is seen in the provision of an alternative last step of the multi step process for the preparation of tibolone of formula 1.

Prior art D4 or D5 can be considered to be the closest prior art. Both documents disclose a hydrolysis of 3-keto group protected in the form of 3,3-dimethylacetal, whereas the process of the present claim 1 comprises hydrolysing of keto-group protected in the form of 3,3-cyclic ketal of formula 2.

The solution is seen in a provision of hydrolysis of 3,3-cyclic ketals of formula 2 instead of 3,3-acyclic ketals in the presence of salts of certain metals.

The use of salts of transition metals or salts of magnesium or lithium is technical feature of the hydrolysing step which is considered novel and inventive, as this technical feature has not been found in the prior art. Furthermore, the present Examples 3 and 4 demonstrate that the use of $CuSO_4$ leads to a higher molar excess of the desired tibolone.

Therefore, the subject-matter of claims 1-9 do involve an inventive step, according to Article 33(3) PCT.

CLAIMS

1. A process for the preparation of 17β-hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yn-3-one of formula 1, which comprises:

(a) hydrolyzing 17β-hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yne 3,3-cyclic ketals of formula 2, where:

(1) each of R_1, R_2, R_3 and R_4 is a hydrogen atom or a C_{1-4} alkyl group, or

(2) R_1 and R_3 are taken together to form an alicyclic ring together with the carbon atoms in the dioxolane ring to which the groups are attached and R_2, R_4 are hydrogen atoms, or

(3) R_1 and R_3 are taken together to form an aromatic ring together with the carbon atoms in the dioxolane ring to which they are attached, and R_2, R_4 are taken together to form a chemical bond participating in the aromatic electron system of the aromatic ring formed by R_1 and R_3;

in the presence of salts of transition metals, salts of lithium or salts of magnesium;

(b). separating 17β-hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yn-3-one obtained in step (a) from 17β-hydroxy-7α-methyl-19-nor-17α-pregn-4-en-20-yn-3-one by-product of formula 3; and

(c) converting 17β-hydroxy-7α-methyl-19-nor-17α-pregn-4-en-20-yn-3-one obtained as a by-product in step (b)

to the ketal of formula 2, wherein R_1-R_4 are defined as above, which is then hydrolyzed to 17β-hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yn-3-one in step (a).

2. A process according to claim 1, which in step (a) comprises hydrolyzing 3,3-ethylenedioxy-17β-hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yne.

3. A process according to claim 2, characterized in that 17β-hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yn-3-one is obtained in a molar excess to 17β-hydroxy-7α-methyl-19-nor-17α-pregn-4-en-20-yn-3-one equal at least 4:1.

4. A process according to claim 3, characterized in that 17β-hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yn-3-one is obtained in a molar excess to 17β-hydroxy-7α-methyl-19-nor-17α-pregn-4-en-20-yn-3-one equal at least 8:1.

5. A process according to claim 1, where the metal salt used in step (a) is copper(II) sulfate.

6. A process according to claims 1-5, characterized in that the hydrolysis reaction is carried out in a mixture of solvents containing 0%-99% water, 0%-100% of an organic solvent selected from a group consisting of THF, $CHCl_3$, 1,4-dioxane, CH_2Cl_2, acetone, acetonitrile, ethylmethylketone, diethylketone, 1,3-dioxolane, 1,2-dimethoxyethane, 1,2-diethoxyethane, and 0%-100% of a C_{1-4} alcohol.

7. A process according to claims 1-6, where the reaction temperature is from about 0°C to about 200°C.

8. A process according to claim 1, characterized in that 17β-hydroxy-7α-methyl-19-nor-17α-pregn-4-en-20-yn-3-one of formula 3 is in step (c) converted to a 17β-hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yne 3,3-ketal of formula 2 by reaction with a vicinal diol of the formula $R_1R_2C(OH)-C(OH)R_3R_4$, in the presence of a protic acid and a hydrocarbon solvent.

9. A process according to claims 1 and 8, characterized in that the 17β-hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yne 3,3-ketal of formula 2, obtained in step (c), is substantially purified before the hydrolysis step (a), by crystallization from a mixture of organic solvents containing 50%-100% ethyl acetate.

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